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## Reduction of a Mechanistic Drying Model of Pharmaceutical Granules for Inclusion in a Population Balance Model with Continuous Growth Term

**Monday, October 29, 2012: 8:30 AM**

[Conference B \(Omni\)](#)

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Nowadays, there is a trend to move from batch towards continuous production processes in the pharmaceutical industry (Leuenberger, 2001). To accomplish this transition properly, all consecutive unit operations executed during the continuous manufacturing should be understood in detail to design adequate control strategies for guaranteeing product quality at all time. Adequate control mechanisms should rely on in-process measurements of critical process and product parameters and real-time adjustment of input variables which are able to direct the process in the right way.

Pharmaceutical processes often consist of multi-phase systems with high complexity. Developing mechanistic models of these multi-phase systems is a means of mapping the detailed knowledge available for such a process (Mortier et al., 2011). Such a modelling approach has only recently started to become more popular in the pharmaceutical area. It has been recognized that the use of mechanistic models and system-based approaches are important for Process Analytical Technology (PAT) and a Quality By Design (QbD) (Sin et al., 2008; Gernaey et al., 2012).

The work presented here resides in the modeling of a continuous fluidized bed drying process, which is used to dry the wet granules originating from the continuous granulator. The ConsiGma<sup>TM</sup> from Collette<sup>TM</sup> (GEA Pharma Systems) is a full continuous from powder to tablet manufacturing line, including a six-segmented fluidized bed drying unit. The drying behaviour of single pharmaceutical granules was previously unraveled in a modeling study including calibration and validation (Mortier et al., 2012). The drying of the wet granules occurs in two subsequent phases. The first drying phase includes the water at the free surface of the droplet. As soon as the radius of the droplet equals the radius of the dry particle, the evaporation rate slows down and the second drying phase begins.

Population Balance Modelling (PBM) is a modeling framework allowing to describe the behaviour of a population of particles with a distributed property. In the case under study, the latter is the moisture content and the evolution of the moisture content distribution for a batch of wet granules is envisioned. The general Population Balance Equation (PBE) can here be simplified into a homogeneous equation solely with a negative continuous growth term expressing the drying. A good candidate for this drying process model is that of a single granule. However, this model is too complicated to integrate it straight away into the PBM. Hence, a model reduction step is required. Different available methods described in the literature were evaluated, e.g. heuristic methods (Van Nes et al., 2005), mathematical based methods (projection based (Bernhardt, 2008), Krylov-based approximation (Antoulas, 2005), sensitivity based methods (Lawrie et al., 2007)). These methods are very case specific and could not be used here.

Therefore, a new strategy was developed for this particular case. It consists of a Global Sensitivity Analysis (GSA) followed by a model reduction step. The GSA is performed to determine the most important parameters and model inputs that need to be retained in the reduced model. Based on the GSA the gas temperature was found to be the most sensitive parameter, and was retained in the model reduction. Details of the GSA are the subject of a separate abstract.

The reduced model needs to be able to describe the decrease of the moisture content for a drying particle. Analysis revealed that the growth term of both drying phases displayed a different behaviour, and that the growth term is strongly dependent on the wet radius, which is a representation of the moisture content. Finally, a size dependent growth term for both drying phases was developed separately. The model reduction starts with collecting data by simulating the full model for a vast range of the selected degree of freedom, i.e. the gas temperature. Simulation at an intermediate value was chosen to reveal the model structure of the reduced empirical model. Subsequently, this structure is verified for all other simulations in the range to ensure the structure is able to describe the behaviour for all values of the degree of freedom in the range. The selected model structure contains a number of parameters, which are calibrated for each simulation by minimizing the Root Mean Square Error (RMSE). In a next step, dependencies (submodel structures) between these parameters and the selected degree of freedom (gas temperature) are determined. The latter was done in a step-wise approach, and upon introducing each new submodel the remaining coefficients are recalibrated. This eventually results in an empirical model solely function of gas temperature, and which can be implemented easily in a PBM. The reduced model consists of two sets of algebraic equations, one for each drying phase, and can be used to solve the Population Balance Equation (PBE) for different gas temperatures, different sizes of the granule and different initial conditions. For the first drying period a mean weighted relative error of 0.53% was obtained compared to the detailed mechanistic drying model, whereas for the second drying period 1.97% was obtained. The latter is an acceptable error given the reduction in complexity.

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